Remarks

Reconsideration of this Application is respectfully requested.

Claims 28-60 are pending in the application, with claims 28-31 being the independent claims.

Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Rejections Under 35 U.S.C. § 103

A. Legal Principles

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.
>
> The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

M.P.E.P. § 2143 ("Basic Requirements of a *Prima Facie* Case of Obviousness") (August 2001). *See also In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988) ("The consistent criterion for determination of obviousness is whether the prior art would have

suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success viewed in light of the prior art.")

B. Claims 28-44, 46, 49-51, 53, 55, 56 and 58-60

The Examiner has rejected claims 28-44, 46, 49-51, 53, 55, 56, and 58-60 under 35 U.S.C. § 103(a) over Foulkes *et al.* (PCT International Publication WO 92/13063, published August 6, 1992) in view of Fodor *et al.* (U.S. Patent No. 6,309,822 B1, issued October 30, 2001). Office Action, page 3, lines 5-7. Applicants respectfully traverse this rejection.

1. The Primary Reference: Foulkes et al.

The Examiner asserts that Foulkes *et al.* teaches all of the limitations of claims 28-44, 46, 49-51, 53, 55, 56, and 58-60 (*see* Office Action, page 3, line 8, through page 5, line 12) except that "Foulkes *et al.* do not teach the method wherein the biological target molecules are receptor proteins" (Office Action, page 5, lines 13-14). Applicants respectfully disagree.

The screening methods disclosed by Foulkes *et al.* are methods "of determining whether a molecule not previously known to be a modulator of protein biosynthesis is capable of *transcriptionally modulating* the expression of a *gene encoding a growth factor*" (*see, e.g.,* page 32, lines 17-21, page 33, lines 12-16, page 34, lines 4-8) (emphasis added). The methods of Foulkes *et al.* are very carefully designed to detect biologically active agents having three specific characteristics:

(a) the detected agent "does not naturally occur in the cell";

(b) the detected agent "*specifically transcriptionally modulates* expression of *the gene encoding a growth factor*"; and

(c) the detected agent "binds to DNA or RNA, or binds to a protein at a site on such protein *which is not a ligand-binding domain of a receptor which naturally occurs in the cell.*"

Foulkes *et al.*, page 15, lines 12-18; page 15, line 33, through page 16, line 4; in claim 1, at page 82, lines 12-18; and in claim 2, at page 82, line 32, through page 83, line 3 (emphasis added).

It follows that the method of Foulkes *et al.* is specifically designed to avoid the detection of any biologically active agent that modulates the expression of a gene by means other than specific transcriptional modulation. The method of Foulkes *et al.* is therefore necessarily designed to avoid the detection of any biologically active agent that modulates the expression of a gene by directly affecting a biological target molecule that is a receptor protein. This avoidance is a necessary consequence of the method of Foulkes *et al.* regardless of whether transcriptional modulation is "direct" or "indirect." *See* Foulkes *et al.* page 27, lines 11-16, and page 28, lines 3-12, respectively.

In the words of Foulkes *et al.*, the detected agent "binds to DNA or RNA, or binds to a protein at a site on such protein which is not a ligand-binding domain of a receptor which naturally occurs in the cell." Foulkes *et al.* page 15, lines16-18; page 16, lines 1-4; in claim 1, at page 82, lines 15-18; and in claim 2, at page 82, line 35, through page 83, line 3.

In contrast to the methods of Foulkes *et al.*, the methods of the present invention are expressly designed for the detection of an agent that effects the activity of a biological target molecule that is a receptor protein (*see* independent claims 28-31, as amended). Claims 32-

44, 46, 49-51, 53, 55, 56 and 58-60 are directly or indirectly dependent upon one or more of independent claims 28-31. Therefore, claims 28-44, 46, 49-51, 53, 55, 56, and 58-60 are not obvious in view of Foulkes *et al.* The deficiencies in Foulkes *et al.* are not cured by the other references cited by the Examiner.

2. The Secondary Reference: Fodor et al.

The Examiner is of the opinion that:

> Fodor et al[.] teach the method wherein the biological target molecules are receptor proteins such as HER2 and Ras. (Column 5, lines 44-62).
>
> It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the receptors HER2 and Ras of Fodor et al. in the process of Foulkes et al., since Fodor et al. state, "Such genes include, but are not limited to the HER2 proto-oncogene in the case of breast cancer, receptor tyrosine kinase (RTKs) associated with the etiology of a number of tumors including carcinomas in the breast, liver, bladder, pancreas, as well as glioblastomas, sarcomas, and squamous carcinomas, and tumor suppressor genes such as the p53 gene and other "marker" genes such as RAS, MSH2, MLH1 and BRCA1 (Column 5, lines 48-55)".

Office Action, page 5, line 15, through page 6, line 4. Applicants respectfully disagree.

Fodor *et al.* teaches "methods for comparing and identifying differences in nucleic acid sequences using a plurality of sequence specific recognition reagents (i.e., probes comprising a nucleic acid complementary to a nucleic acid sequence in collections to be compared) bound to a solid surface" (*see* the Abstract). Fodor *et al.* also discloses the existence of the HER2 and RAS *genes*. At no point in the passage cited by the Examiner is the existence of a HER2 or RAS receptor mentioned. Therefore, claims 28-44, 46, 49-51,

53, 55, 56, and 58-60 are not obvious in view of Fodor *et al.* and the other references cited by the Examiner.

Additionally, the discussion in Fodor *et al.* (col. 5, lines 48-55) regarding "marker genes" does not provide any motivation to modify Foulkes *et al.* in view of Fodor *et al.* Furthermore, the Examiner has not explained why the proposed combination would have a reasonable likelihood of success, when viewed from the perspective of one of ordinary skill in the art at the time the invention was made. Therefore, the Examiner has not established a *prima facie* case for the rejection of claims 28-44, 46, 49-51, 53, 55, 56, and 58-60 under 35 U.S.C. § 103(a).

Finally, the Examiner's attempt to modify Foulkes *et al.* in view of Fodor *et al.* to arrive at Applicants' invention, necessarily requires that the invention of Foulkes *et al.* be changed so as to determine the pharmacological effect of a substance on a biological target molecule that is a receptor protein. The detection of the pharmacological effect of a substance on a biological target molecule that is a receptor protein is expressly prohibited by the invention of Foulkes *et al.* Therefore, Fodor *et al.* is disqualified as a reference. "If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984)." M.P.E.P. page 2100-124, col. 2, lines 30-34.

3. Summary

Applicants respectfully submit that the rejection of claims 28-44, 46, 49-51, 53, 55, 56, and 58-60 under 35 U.S.C. § 103(a) has been overcome and should be withdrawn.

C. Claim 57

The Examiner has rejected claim 57 under 35 U.S.C. § 103(a) over Foulkes *et al.* in view of Fodor *et al.* and further in view of Chapman *et al.* (U.S. Patent No. 6,232,099 B1, issued May 15, 2001). Office Action, page 6, lines 11-14. Applicants respectfully traverse this rejection.

Specifically, the Examiner is of the opinion that:

> Foulkes et al[.] in view of Fodor et al. teach the process of claims 28-44, 46, 49-51, 53, 55-56, and 58-60 as described above.
>
> Foulkes et al[.] in view of Fodor et al. do not teach the Green fluorescent protein as the reporter gene.
>
> Chapman et al[.] teach the Green fluorescent protein as the reporter gene (Examples 1 and 2 and Figures 1a and 1b).
>
> It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the Green fluorescent protein of Chapman et al. in the process of Foulkes et al. in view of Fodor et al., since Chapman et al. state, "The green fluorescent protein (GFP) from A. Victoria is a reporter of gene expression in heterologous systems. GFP has an advantage over other marker proteins in that it can be detected non-invasively, without any requirement for exogenous substrates or co-factors since it fluoresces intrinsically without a requirement for exogenous substrate. In addition, fluorescence of GFP is

> retained in fusion proteins allowing the subcellular localization of fusion proteins (Column 7, line 66 to column 8, line 7)."

Office Action, page 6, line 15, through page 7, line 9. Applicants respectfully disagree.

Chapman *et al.* teach " [a] method of producing a chimeric protein from ie a plant virus coding for such a protein" (Abstract, first sentence) and a "vector for the production of biologically useful proteins" (Abstract, last sentence).

The Examiner's statement that "[a]n ordinary practitioner would have been motivated to combine and substitute the Green fluorescent protein of Chapman et al. in the process of Foulkes et al. in view of Fodor et al. in order to improve the process for determining the pharmacological effect of a substance on a cell" (Office Action, page 7, lines 9-12) is entirely conclusory and points to no motivation to combine any of the references cited by the Examiner. Furthermore, the Examiner has not documented any reason why one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for the combination of the teachings of Foulkes *et al.*, Fodor *et al.* and Chapman *et al.* Therefore, the Examiner has not satisfied his burden for the establishment of a *prima facie* case of obviousness with regard to claim 57.

It has been demonstrated in section I.B., above that Foulkes *et al.* in view of Fodor *et al.* does not teach all of the limitations of independent claims 28-31. Claim 57 is multiply and indirectly dependent upon claims 28-31, therefore claim 57 is not obvious – regardless of whether Chapman *et al.* does or does not teach the Green fluorescent protein.

Finally, the Examiner's attempt to modify Foulkes *et al.* in view of Fodor *et al.* and further in view of Chapman *et al.* to arrive at Applicants' invention, necessarily requires that the invention of Foulkes *et al.* be changed so as to determine the pharmacological effect of a substance on a biological target molecule that is a receptor protein. The detection of the

pharmacological effect of a substance on a biological target molecule that is a receptor protein is expressly prohibited by the invention of Foulkes *et al.* Therefore, Chapman *et al.* is disqualified as a reference.

For the reasons stated above, Applicants respectfully submit that the rejection of claim 57 under 35 U.S.C. § 103(a) has been overcome and should be withdrawn.

D. Claim 45

The Examiner has rejected claim 45 under 35 U.S.C. § 103(a) over Foulkes *et al.* in view of Fodor *et al.* and further in view of Bilodeau *et al.* (U.S. Patent No. 6,235,741 B1, issued May 22, 2001). Office Action, page 7, lines 17-20. Applicants respectfully traverse this rejection.

Specifically, the Examiner is of the opinion that:

> Foulkes et al[.] in view of Fodor et al. teach the process of claims 28-42, 44, 46, 49-50, 53, 55-56, and 58-60 as described above.
>
> Foulkes et al[.] in view of Fodor et al. do not teach the receptor KDR.
>
> Bilodeau et al[.] teach the receptor KDR. (Column 2, lines 1-16).
>
> It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the receptors KDR of Bilodeau et al. in the process of Foulkes et al. in view of Fodor et al., since Bilodeau et al. state, "Inhibition of KDR or Flt-1 is implicated in pathological neoangiogenesis, and these are useful in the treatment of diseases in which neoangiogenesis is part of the overall pathology, e.g., diabetic retinal vascularization, as well as various forms of cancer (Column 2, lines 12-16))".

Office Action, page 8, lines 1-10. Applicants respectfully disagree.

Bilodeau *et al.* teach "compounds which inhibit tyrosine kinase enzymes, compositions which contain tyrosine kinase inhibiting compounds and methods of using tyrosine kinase inhibitors to treat tyrosine kinase-dependent diseases/conditions such as angiogenesis, cancer, atherosclerosis, diabetic retinopathy or autoimmune diseases, in mammals." Bilodeau *et al.*, Abstract, lines 1-7. Bilodeau *et al.* teach that KDR and Flt-1 are tyrosine kinase receptors (*see* col. 1, lines 34-35). Bilodeau *et al.* also teach that "inhibition of KDR or Flt-1 is implicated in pathological neoangiogenesis, and these [*i.e.*, compounds that inhibit KDR or Flt-1] are useful in the treatment of diseases in which neoangiogenesis is part of the overall pathology, e.g., diabetic retinal vascularization, as well as various forms of cancer" (*see* col. 2, lines 12-16).

Bilodeau *et al.* arguably suggest that would be desirable for medical researchers to possess compounds that inhibit KDR. Such a generalized desire is merely an invitation to conduct research and not a motivation to combine Bilodeau *et al.* with any other reference.

The Examiner's statement that "[a]n ordinary practitioner would have been motivated to combine and substitute the receptors KDR of Bilodeau et al. in the process of Foulkes et al. in view of Fodor et al., in order to improve the process for determining the pharmacological effect of a substance on a cell" (Office Action, page 8, lines 10-13) is entirely conclusory and points to no motivation to combine any of the references cited by the Examiner. Furthermore, the Examiner has not documented any reason why one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for the combination of the teachings of Foulkes *et al.*, Fodor *et al.* and Bilodeau

et al. Therefore, the Examiner has not satisfied his burden for the establishment of a *prima facie* case of obviousness with regard to claim 45.

It has been demonstrated in section I.B., above that Foulkes *et al.* in view of Fodor *et al.* does not teach all of the limitations of independent claims 28-31. Claim 45 is multiply and indirectly dependent upon claims 28-31, therefore claim 45 is not obvious – regardless of whether Bilodeau *et al.* does or does not teach the KDR receptor.

Finally, as was the case for Chapman *et al.* (*see* section I.C., paragraph 6, above), Bilodeau *et al.* is disqualified as a reference.

For the reasons stated above, Applicants respectfully submit that the rejection of claim 45 under 35 U.S.C. § 103(a) has been overcome and should be withdrawn.

E. Claim 47

The Examiner has rejected claim 47 under 35 U.S.C. § 103(a) over Foulkes *et al.* in view of Fodor *et al.* and further in view of Nishi *et al.* (U.S. Patent No. 6,159,967, issued December 12, 2000). Office Action, page 8, line 18, through page 9, line 2. Applicants respectfully traverse this rejection.

Specifically, the Examiner is of the opinion that:

> Foulkes et al[.] in view of Fodor et al. teach the process of claims 28-44, 46, 49-51, 53, 55-56, and 58-60 as described above.
>
> Foulkes et al[.] in view of Fodor et al. do not teach the neurokinin receptor.
>
> Nishi et al[.] teach the neurokinin receptor. (Column 1, lines 30-40 and Column 244, line 65 to column 245, line 42).

> It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the neurokinin receptor of Nishi et al. in the process of Foulkes et al. in view of Fodor et al., since Nishi et al. state, "The novel compounds of the present invention have a superior antagonistic effect on substance P and neurokinin receptors. Moreover since they have low toxicity, they are useful for the prevention and therapy of tachykinin-mediated diseases, examples of which include diseases of the central nervous system including anxiety, depression, psychosis and schizophrenia (Column 224, line 65 to column 245, line 5)."

Office Action, page 9, lines 3-15. Applicants respectfully disagree.

Nishi *et al.* teach a genus of chemical compounds that "have tachykinin receptor antagonist activity and exhibit an activity against both the NK_1 and NK_2 receptors." Nishi *et al.*, Abstract, last sentence. The Examiner cites Nishi *et al.* for the proposition that "[t]he *novel compounds* of the present invention [U.S. Patent No. 6,159,967] have a superior antagonistic effect on substance P and neurokinin receptors. Moreover since they have low toxicity, they are useful for the prevention and therapy of tachykinin-mediated diseases, examples of which include diseases of the central nervous system including anxiety, depression, psychosis and schizophrenia." Office Action, page 9, lines 10-14, quoting Nishi *et al.*, col. 244, line 65, through col. 245, line 5 (emphasis added). Thus, the only advantages taught by Nishi *et al.* are advantages attributed to the claimed chemical compounds which are irrelevant to Applicants' invention.

Nishi *et al.* arguably suggest that would be desirable for medical researchers to possess compounds that inhibit the neurokinin receptor. Such a generalized desire is merely an invitation to conduct research and not a motivation to combine Nishi *et al.* with any other reference.

The Examiner's statement that "[a]n ordinary practitioner would have been motivated to combine and substitute the neurokinin receptor of Nishi et al. in the process of Foulkes et al. in view of Fodor et al., in order to improve the process for determining the pharmacological effect of a substance on a cell" (Office Action, page 9, lines 15-17) is entirely conclusory and points to no motivation to combine any of the references cited by the Examiner. Furthermore, the Examiner has not documented any reason why one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for the combination of the teachings of Foulkes *et al.*, Fodor *et al.* and Nishi *et al.* Therefore the examiner has not satisfied his burden for the establishment of a *prima facie* case of obviousness with regard to claim 47.

It has been demonstrated in section I.B., above, that Foulkes *et al.* in view of Fodor *et al.* does not teach all of the limitations of independent claims 28-31. Claim 47 is multiply and indirectly dependent upon claims 28-31, therefore claim 47 is not obvious – regardless of whether Nishi *et al.* does or does not teach the neurokinin receptor.

Finally, as was the case for Chapman *et al.* (*see* section I.C., paragraph 6, above), Nishi *et al.* is disqualified as a reference.

For the reasons stated above, Applicants respectfully submit that the rejection of claim 48 under 35 U.S.C. § 103(a) has been overcome and should be withdrawn.

F. Claim 48

The Examiner has rejected claim 48 under 35 U.S.C. § 103(a) over Foulkes *et al.* in view of Fodor *et al.* and further in view of Gerald *et al.* (U.S. Patent No. 6,331,401, issued

December 18, 2001). Office Action, page 10, lines 1-4. Applicants respectfully traverse this rejection.

Specifically, the Examiner is of the opinion that:

> Foulkes et al[.] in view of Fodor et al. teach the process of claims 28-44, 46, 49-51, 53, 55-56, and 58-60 as described above.
>
> Foulkes et al[.] in view of Fodor et al. do not teach the serotonin receptor.
>
> Gerald et al[.] teach the serotonin receptor. (Column 21, lines 16-50).
>
> It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the serotonin receptor of Gerald et al. in the process of Foulkes et al. in view of Fodor et al., since Gerald et al. state, "Analysis of 5-HT4 structure and function provides a model for the development of drugs useful for the treatment of gastrointestinal conditions including bowel disease, postoperative ileus, diabetic gastroparesis, emesis, achalesia, hiatal hernia, and esophageal spasm (Column 121, lines 22-27)".

Office Action, page 10, lines 5-14. Applicants respectfully disagree.

In support of this rejection, the Examiner quotes Gerald *et al.* for the proposition that "[a]nalysis of 5-HT4 structure and function provides *a model for the development of drugs* useful for the treatment of gastrointestinal conditions including bowel disease, postoperative ileus, diabetic gastroparesis, emesis, achalesia, hiatal hernia, and esophageal spasm." (Office Action, page 10, lines 11-14, quoting Gerald *et al.*, col. 21, lines 22-27) (emphasis added).

Contrary to the Examiner's interpretation, this quotation from Gerald *et al.* is merely an invitation to conduct research. A combination of the teachings of Gerald *et al.* with those of Foulkes *et al.* and Fodor *et al.* is, at most, "obvious to try"; and this is not a sufficient reason for the Examiner to combine these teachings. *See In re Fine* 837 F.2d 1071 (Fed. Cir.

1988) ("Whether a particular combination might be 'obvious to try' is not a legitimate test of patentability.").

Gerald *et al.* arguably suggests that it would be desirable for medical researchers to possess compounds that inhibit the 5-HT_4 (serotonin) receptor. Such a generalized desire is merely an invitation to conduct research and not a motivation to combine Gerald *et al.* with any other reference.

Additionally, the Examiner's statement that "[a]n ordinary practitioner would have been motivated to combine and substitute the serotonin receptor of Gerald et al. in the process of Foulkes et al. in view of Fodor et al., in order to improve the process for determining the pharmacological effect of a substance on a cell" (Office Action, page 10, lines 14-17) is entirely conclusory and points to no motivation to combine any of the references cited by the Examiner. Furthermore, the Examiner has not documented any reason why one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for the combination of the teachings of Foulkes *et al.*, Fodor *et al.* and Gerald *et al.* Therefore the examiner has not satisfied his burden for the establishment of a *prima facie* case of obviousness with regard to claim 48.

It has been demonstrated in section I.B., above that Foulkes *et al.* in view of Fodor *et al.* does not teach all of the limitations of independent claims 28-31. Claim 48 is multiply and indirectly dependent upon claims 28-31, therefore claim 48 is not obvious – regardless of whether Gerald *et al.* does or does not teach the seratonin receptor.

Finally, as was the case for Chapman *et al.* (*see* section I.C., paragraph 6, above), Gerald *et al.* is disqualified as a reference.

For the reasons stated above, Applicants respectfully submit that the rejection of claim 48 under 35 U.S.C. § 103(a) has been overcome and should be withdrawn.

G. Claim 52

The Examiner has rejected claim 52 under 35 U.S.C. § 103(a) over Foulkes *et al.* in view of Fodor *et al.* "further in view of Johnson (U.S. Patent 6,331,170 [sic, 6,333,170] B1) (December 25, 2001)." Office Action, page 11, lines 3-6. Applicants respectfully traverse this rejection.

Specifically, the Examiner is of the opinion that:

> Foulkes et al[.] in view of Fodor et al. teach the process of claims 28-44, 46, 49-51, 53, 55-56, and 58-60 as described above.
>
> Foulkes et al[.] in view of Fodor et al. do not teach the Raf receptor.
>
> Johnson teaches the Raf receptor. (Column 5, lines 11-18).
>
> It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the Raf receptor of Johnson in the process of Foulkes et al. in view of Fodor et al., since Johnson states, "In particular, the method comprises regulating the apoptosis of the cell. Such a method is useful for the treatment of a medical disorder. In particular, the method is useful for inhibiting tumorigenesis and autoimmunity (Column 5, lines 14-18)".

Office Action, page 11, lines 7-16. Applicants respectfully disagree.

The full paragraph, quoted immediately above, discusses MEKK-dependent *pathways* and Raf-dependent *pathways*. The passage quoted by the Examiner does not teach the Raf-

receptor. Thus, the teaching of Johnson does not cure the deficiency, perceived by the Examiner, in the teaching of Foulkes *et al.* in view of Fodor *et al.* Therefore the examiner has not satisfied his burden for the establishment of a *prima facie* case of obviousness with regard to claim 52.

In addition, the passage quoted by the Examiner does not provide any motivation for one of ordinary skill in the art to combine the teaching of Johnson with that of Foulkes *et al.* in view of Fodor *et al.* Furthermore, the Examiner has not documented any reasonable expectation of success for the proposed combination. Therefore, the Examiner has not satisfied his burden for the establishment of a *prima facie* case of obviousness with regard to claim 52.

The Examiner's statement that "[a]n ordinary paractitioner would have been motivated to combine and substitute the Raf receptor of Johnson in the process of Foulkes et al. in view of Fodor et al. [], in order to improve the process for determining the pharmacological effect of a substance on a cell" (Office Action, page 11, lines 16-19) is entirely conclusory and points to no motivation to combine any of the references cited by the Examiner.

Furthermore, this embodiment of Johnson can not function in the absence of a comparative change in the activity of a MEKK-dependent pathway *relative to* the activity of a Raf-dependent pathway in the cell. Therefore, exporting the raf-dependent pathway of Johnson (or any part thereof) in the absence of a MEKK-dependent pathway would render the teaching of Johnson unsatisfactory for its intended purpose. "If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification." M.P.E.P., page 2100-124, col. 2, lines 30-34 (*citing In re Gordon*, 733 F.2d 900, 221 USPQ 1123 (Fed.

Cir. 1984)). Since there is no suggestion or motivation to make the proposed modification, the Examiner has not satisfied his burden for the establishment of a *prima facie* case of obviousness with regard to claim 52.

It has been demonstrated in section I.B., above that Foulkes *et al.* in view of Fodor *et al.* does not teach all of the limitations of independent claims 28-31. Claim 52 is multiply and indirectly dependent upon claims 28-31. Ttherefore, claim 52 is not obvious – regardless of whether Johnson does or does not teach the Raf receptor.

Finally, as was the case for Chapman *et al.* (*see* section I.C., paragraph 6, above), Johnson is disqualified as a reference.

For the reasons stated above, Applicants respectfully submit that the rejection of claim 52 under 35 U.S.C. § 103(a) has been overcome and should be withdrawn.

H. Claim 54

The Examiner has rejected claim 54 under 35 U.S.C. § 103(a) over Foulkes *et al.* in view of Fodor *et al.* further in view of O'Hare *et al.* (U.S. Patent No. 6,017,735, issued January 15, 2000). Office Action, page 12, lines 3-6. Applicants respectfully traverse this rejection.

Specifically, the Examiner is of the opinion that:

> Foulkes et al[.] in view of Fodor et al. teach the process of claims 28-44, 46, 49-51, 53, 55-56, and 58-60 as described above.
>
> Foulkes et al[.] in view of Fodor et al. do not teach the bcl-2 receptor.

> O'Hare et al. teach the bcl-2 receptor. (Column 7, lines 4-8).
>
> It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the bcl-2 receptor of O'Hare et al. in the process of Foulkes et al. in view of Fodor et al., since O'Hare et al. state, "Known proteins of the bcl2 family, such as bcl2 itself, bcl-XL, or bclw, to mask or inhibit apoptosis where this is desired, e.g., in treatment of neurodegeneration (Column 7, lines 5-8)".

Office Action, page 12, lines 7-15. Applicants respectfully disagree.

O'Hare *et al.* teach:

> Coupled polypeptides and fusion polypeptides for intracellular transport, and their preparation and use, include (i) an aminoacid sequence with the transport function of herpes-viral VP22 protein (or a homologue, e.g. from VZV, BHV or MDV) and (ii) another protein sequence selected from (a) proteins for cell cycle control; (b) suicide proteins; (c) antigenic sequences or antigenic proteins from microbial and viral antigens and tumour antigens; (d) immunomodulating proteins; and (e) therapeutic proteins. The coupled proteins can be used for intracellular delivery of protein sequences (ii), to exert the corresponding effector function in the target cell, and the fusion polypeptides can be expressed from corresponding polynucleotides, vectors and host cells.

O'Hare *et al.*, Abstract, lines 1-13.

O'Hare *et al.* describes one embodiment at col. 6, line 64, through col. 7, line 8. The Examiner has quoted only the third sentences, thereof. The complete paragraph is as follows:

> *VFP22 coupling products* can also usefully be used in the modulation of apoptosis, e.g. to induce cell death, of the apoptosis type, by the introduction into a cell of a protein apoptotic domain *coupled to VP22*, such as e.g. apoptosis protein bax, or its known identified apoptosis inducing peptide; or known related protein bad or bak. Here too the *coupling product* can be applied in the form either of protein

> or DNA encoding it. *VPP coupling products* can be used in the form of VP22 with known proteins of the bc12 family, such as bcl2 itself, bcl-xL, or bclw, to mask or inhibit apoptosis where this is desired, e.g in treatment of neurodegeneration.

O'Hare et al. col. 6, line 64, through col. 7, line 8 (emphasis added).

First, the quoted paragraph discusses VFP22 *coupled products*, including VFP22 *coupled products* "in the form of *VP22 with known proteins* of the bc12 family." The quoted paragraph does not teach the bcl-2 *receptor*. Thus, O'Hare *et al.* does not cure the deficiency, perceived by the Examiner, in the teaching of Foulkes *et al.* in view of Fodor *et al.* Therefore, the Examiner has not satisfied his burden for the establishment of a *prima facie* case of obviousness with regard to claim 54.

In addition, the passage quoted by the Examiner does not provide any motivation for one of ordinary skill in the art to combine the teaching of O'Hare *et al.* with that of Foulkes *et al.* in view of Fodor *et al.* Furthermore, the Examiner has not documented any reasonable expectation of success for the proposed combination. Therefore, the Examiner has not satisfied his burden for the establishment of a *prima facie* case of obviousness with regard to claim 54.

The Examiner's statement that "[a]n ordinary paractitioner would have been motivated to combine and substitute the bcl-2 receptor of O'Hare *et al.* in the process of Foulkes et al. in view of Fodor et al., in order to improve the process for determining the pharmacological effect of a substance on a cell" (Office Action, page 12, lines 15-18) is entirely conclusory and points to no motivation to combine O'Hare *et al.* with any other reference.

It has been demonstrated in section I.B., above that Foulkes *et al.* in view of Fodor *et al.* does not teach all of the limitations of independent claims 28-31. Claim 54 is multiply and indirectly dependent upon claims 28-31, therefore claim 54 is not obvious – regardless of whether O'Hare *et al.* does or does not teach the bcl-2 receptor.

Finally, as was the case for Chapman *et al.* (*see* section I.C., paragraph 6, above), O'Hare *et al.* is disqualified as a reference.

For the reasons stated above, Applicants respectfully submit that the rejection of claim 54 under 35 U.S.C. § 103(a) has been overcome and should be withdrawn.

II. The Examiner's Response to Amendment and Response to Argument

The Examiner states that "In response to amendment, all 112 (second paragraph) rejections and 102(b) [rejections] are hereby withdrawn. New 103(a) rejections based on the same prior art are hereby included." Office Action, "Response to Amendment," page 13, lines 1-3.

All of the rejections contained in the present Office Action are new rejections. Thus, there would appear to be no reason for the Examiner to record a response to Applicants arguments against previous rejections that do not now exist, as the Examiner has done in the present Office Action. *See* Office Action, "Response to Arguments," page 13, line 8, through page 14, line 4. Applicants do not here argue the merits of non-existent rejections. Applicants do traverse the Examiner's comments in the Office Action at page 13, line 8, through page 14, line 4, and expressly reserve all rights regarding prosecution of the above-captioned application.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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